Solesta® Injectable Gel

CAUTION: Federal law restricts this device to sale by or on the order of a physician.

INDICATION FOR USE

Solesta® is indicated for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications).

DEVICE DESCRIPTION

Solesta consists of dextranomer microspheres, 50 mg/mL, and stabilized sodium hyaluronate, 15 mg/mL, in phosphate-buffered 0.9% sodium chloride solution.

Solesta is a sterile, viscous, biocompatible bulking agent contained in a disposable 1 mL assembled glass syringe with a standard luer-lock fitting. The syringe is equipped with a plunger stopper, a plunger rod, and a finger grip. The labeled syringe is packed in a pouch and terminally sterilized by moist heat. The final product consists of a carton containing four pouches with syringes, four sterile needles (21G x 4 ¾ inches, 0.80 x 120 mm), and patient record labels. The product is for single use.

Both the dextranomer and sodium hyaluronate are made up of biosynthesized polysaccharides of non-animal origin. The dextranomer component consists of microspheres of dextran chains cross-linked into a three-dimensional network. The stabilized sodium hyaluronate accounts for the viscous properties of Solesta and acts as a carrier that facilitates the injection of the dextranomer microspheres.

Solesta is injected in the deep submucosal layer in the proximal part of the high-pressure zone of the anal canal about 5 mm above the dentate line. A total of four submucosal injections of 1 mL Solesta are administered at each treatment session.

ELECTRONIC IFU

A copy of this Solesta Instructions for Use document in pdf format is available at mysolesta.com by selecting the Physician button and then accessing the RESOURCES tab and scrolling to the Solesta IFU document.

In addition, paper copies of the Solesta IFU may be requested by calling (844) 350-9656. A paper copy will be provided to the requestor within 72 hours.

CONTRAINDICATIONS

Solesta is contraindicated in patients with the following conditions:

- Active inflammatory bowel disease
- Immunodeficiency disorders or ongoing immunosuppressive therapy
- Previous radiation treatment to the pelvic area
- Significant mucosal or full thickness rectal prolapse
- Active anorectal conditions including abscess, fissures, sepsis, bleeding, proctitis, or other infections
- Anorectal atresia, tumors, stenosis, or malformation
- Rectocele
- Rectal varices
- Presence of existing implant (other than Solesta) in anorectal region
- Allergy/hypersensitivity to hyaluronic-acid-based products and/or dextran, or a history of hypersensitivity to streptococcalproteins as the product may contain a trace amount of such material

WARNINGS

- Do not inject Solesta intravascularly. Injection of Solesta into blood vessels may cause vascular occlusion.
- Injection in the midline of the anterior wall of the rectum should be avoided in men with an enlarged prostate.
- If the expiration date or lot number is missing or illegible on the packaging, do not use the product and contact the Palette Life Sciences Medical Information Department.

PRECAUTIONS

General Precautions

- Solesta should only be administered by physicians experienced in performing anorectal procedures and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure.
- The safety and effectiveness of Solesta have not been investigated in patients with complete external sphincter disruption or significant chronic anorectal pain.
- The safety and effectiveness of Solesta have not been investigated in patients with previous procedures involving the anorectal region: rectal anastomosis < 12 cm from anal verge, anorectal surgery within previous 12 months, hemorrhoid treatment with rubber band within 3 months, anorectal implants and/or previous injection therapy other than Solesta, Stapled Transanal Rectal Resection (STARR), or stapled hemorrhoidectomy.
- The safety and effectiveness of Solesta have not been studied in patients under the age of 18 years.
- The safety and effectiveness of Solesta have not been studied in pregnant or breastfeeding women.
- The durability of Solesta has not been studied past 36 months.

Patient-Related Precautions

- Patients with bleeding diathesis or patients using anticoagulant or antiplatelet agents, as with any injections, may experience increased bleeding at injection sites.
- Patients should be counseled that a repeat Solesta injection procedure may be required to achieve a satisfactory level of improvement in incontinence.
- Solesta is radiographically opaque. Patients should be informed that the Solesta implant may be detected during radiographic imaging due to microcalcification and may be misdiagnosed as a cyst, abscess, or tumor. The Solesta Implant Card should be provided to the patient to retain for his or her records.
- Solesta may be palpated on an anorectal or gynecological exam.

Procedure-Related Precautions

- Adequate bowel preparation of the rectum using an enema is required prior to injection. The enema should be given immediately prior to the procedure to ensure evacuation of the anorectum. It is recommended that additional cleansing of the injection area with an antiseptic be performed prior to injection. Use of prophylactic antibiotics is recommended.
- Solesta should be injected slowly to avoid undue stress on the luer-lock connection, which could cause leakage of the gel.
- After injection of Solesta, hold the needle at the injection site for an additional 15-30 seconds to minimize leakage of Solesta.
- Injections too close to the dentate line or too deep in the tissue might cause excessive pain.
- Injection should be stopped if excessive bleeding or pain occurs.
- One sterile needle should be used per syringe and injection.

Device-Related Precautions

- The use of needles other than those supplied may impede injection of Solesta due to the properties of the gel and may cause device malfunction.
- Solesta is supplied ready to use in a prefilled syringe with a luer-lock fitting. Carefully examine the unit to verify that neither the contents nor the package has been damaged in shipment. Do not use if damaged.
- Solesta is supplied sterile and is intended for single use only. Do not re-sterilize, as this may damage or alter the product.
- In the event of accidental contamination of a needle, discard the needle.
- Never mix Solesta with other products.
- Solesta is to be stored at up to 25°C (77°F) and used prior to the expiration date printed on the label. Do not expose Solesta to either sunlight or freezing, as this may damage or alter the product.
- Care should be taken when handling the glass syringes and disposing of broken glass to avoid laceration or other injury.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state, and federal requirements.

ADVERSE EVENTS

The adverse event profile of Solesta was investigated up to 36 months post injection. Adverse events considered possibly or probably related to Solesta treatment include the following events that were experienced by at least 1.5% of patients in the Pivotal Study (Table 5 in the Clinical Studies Section) or the Post-Approval Study (Table 12 in the Post-Approval Study Results Section): proctalgia, injection site hemorrhage, rectal hemorrhage, pyrexia, diarrhea, injection site pain, anorectal discomfort, anal hemorrhage, rectal discharge, proctitis, anal prolapse, constipation, anal pruritus, lower abdominal pain, defecation urgency, painful defecation, rectal obstruction, chills, injection site nodule, pain, rectal abscess, rectovaginal septum abscess, dyspareunia, and alopecia. Adverse events considered possibly or probably related to Solesta treatment and reported for only one patient each are listed in the footnote to Table 5.

The observed adverse events are discussed in the Clinical Studies Section below.

CLINICAL STUDIES

Introduction

Clinical data supporting the safety and effectiveness of Solesta are available from four clinical studies: 1) a pivotal, prospective, multicenter, randomized, sham-controlled double-blind study of 206 patients conducted under an Investigational Device Exemption (IDE; Pivotal Study), 2) a prospective, single-arm, multicenter, observational clinical study of 283 patients conducted under a Post-Approval Study (PAS); 3) a prospective, multicenter, open-label study of 115 patients conducted outside the United States (Open-Label Study), and 4) a single center study of 34 patients conducted at one site in Sweden (Proof-of-Concept Study).The Pivotal Study also included a cross-over option for patients initially randomized to Sham. The majority of patients (over 84%) in all four studies were female.

Table 1 provides an overview of the design of the four studies.

Table 1: Overview of Design of Studies

	Pivotal Study	Post-Approval Study	Open-Label Study	Proof-of-Concept Study
Study Design	Randomized double-blind comparative study of Solesta versus Sham in 2:1 ratio	Open study	Open study	Open study
Primary Efficacy Endpoints	Effectiveness: Superiority in proportion Responder$_{50}$ compared with Sham at 6 months Durability of response based on proportion responders at 12 months Durability of response was also evaluated up to 36 months following last injection	Effectiveness: Freedom from fecal incontinence (FI) re-intervention	Effectiveness: Proportion Responder$_{50}$ at 12 months Durability of response was also evaluated up to 24 months following last injection	Effectiveness: Proportion Responder$_{50}$ at 12 and 24 months

	Pivotal Study	Post-Approval Study	Open-Label Study	Proof-of-Concept Study
Secondary Efficacy Variables	Fecal Incontinence Quality of Life Scale (FIQL)	FIQL	FIQL	SF-36 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30
	Cleveland Clinic Florida Incontinence Score (CCFIS)	CCFIS	CCFIS	Miller Score
	FI-free days	Global Perceived Effect Score	FI-free days	FI-free days
	FI episodes, controlled bowel emptying, medications	Time to FI re-intervention	FI episodes, controlled bowel emptying, medications	FI episodes, global evaluation by patient, patient subjective judgment of treatment effect
Investigational Centers	8 centers in US and 5 centers in Europe	18 centers in US	14 centers in Europe and 1 center in Canada	1 center in Sweden
Sample Size	136 patients randomized to Solesta, and 70 patients randomized to Sham	283 patients	115 patients	34 patients
Inclusion Criteria	Age 18-75 years	Age ≥18 years	Age 18-80 years	Age 18-80 years
	≥4 FI episodes over 14 days in patient diary	FI	≥4 FI episodes over 28 days in patient diary	At least one FI episode weekly
	CCFIS≥10		CCFIS≥5	Miller score ≥6
	Solid or liquid FI episodes		Solid or liquid FI episodes	Solid or liquid FI episodes
	Failed conservative treatment	Failed conservative treatment	Failed conservative treatment	
Exclusion Criteria	Complete external sphincter disruption, Significant mucosal prolapse	Significant mucosal or full thickness rectal prolapse	Complete external sphincter disruption, Significant mucosal prolapse	Complete external sphincter disruption, Significant mucosal prolapse
Retreatment Criteria	Incontinent at one month after initial treatment and CCFIS ≥10	Inadequate response to the initial treatment	Incontinent at one month after initial treatment	Some subjective improvement but less than 50% reduction in FI episodes

The Pivotal Study is the primary data set that demonstrates the safety and effectiveness of Solesta. The Post-Approval Study supports the findings of the Pivotal Study and demonstrates the continued safety and effectiveness of Solesta. The Open-Label and Proof-of-Concept Studies provide supporting evidence of safety and effectiveness. The safety and effectiveness of Solesta have been studied in patients who received one or two treatments. In the Pivotal Study, the majority of patients received two treatments, four weeks apart. In the Post-Approval Study, the majority of patients received two treatments, one to three months apart.

Treatment Information

Pre-Operative Bowel Preparation

Pre-treatment evacuation of the rectum was done with an enema in the majority of the patients in all four studies. A small number of patients received topical antiseptic cleansing at the discretion of the treating physician. Prophylactic antibiotics were administered to individual patients in the Pivotal and Post-Approval Studies at the discretion of the treating investigator. Only 15 patients at three sites in the Pivotal Study and 116 patients in the Post-Approval Study received prophylactic antibiotics. No patients in the Open-Label Study received prophylactic antibiotics.

Treatment Procedure

The Solesta injection procedure was the same in all four studies. Treatment was administered in an out-patient setting without anesthesia. Four equally spaced injections were administered through an anoscope and placed about 5 mm proximal to the dentate line. Treatment volume was generally 4 x 1 mL per treatment session. A single re-treatment procedure was offered to patients with persistent FI after approximately 1 month in the Pivotal Study and from 1 to 3 months in the Post-Approval Study. If a patient received retreatment, the maximum total treatment dose was 8 mL (4 mL per treatment x 2 treatments). In the Pivotal Study, the sham injection procedure consisted of using 4 separate syringes to pierce the mucosa. The syringes were held in place for the same amount of time as a Solesta injection: however, nothing was injected.

Pivotal, Open-Label and Proof-of-Concept Study Results

Patient Demographics

Both the Pivotal and Open-Label Multicenter Studies enrolled patients with a broad range of age and body mass index. The majority of patients enrolled in both studies were females. Over 10% of patients enrolled in the Pivotal Study were African-Americans, Hispanics, or Asians. The causes of FI in both studies were attributed mainly to obstetric cause, neurogenic cause, and iatrogenic cause based on available medical history.

Table 2 provides an overview of the patient demographics in the Pivotal Study. The Open-Label Study and the Proof-of-Concept Study enrolled patients with similar demographics.

Table 2: Demographics in the Pivotal Study

Subject Demographics		**Pivotal Study (n=206)**
Female	n (%)	183 (88.8)
Age, years	Mean (range)	60.1 (29.4–76.0)
Body Mass Index (BMI), kg/m2	Mean (range)	27.1 (17.2–44.8)
Caucasian origin	n (%)	181 (87.9)
Duration of symptoms over 5 years	n (%)	106 (51.7)
Obstetric cause	n (%)	82 (39.8)
Neurogenic cause	n (%)	43 (20.9)
Iatrogenic cause	n (%)	46 (22.3)
Other cause (mostly idiopathic)	n (%)	35 (17.0)

Safety Data

The safety evaluation of Solesta in the treatment of FI is based on the results from the Pivotal Clinical Study and is supported by the Open-Label Multicenter Clinical Study and one single site Proof-of-Concept Study. The analysis of safety was based on the safety cohort of all 206 patients treated in the Pivotal Study with either Solesta or Sham. During the 6-month blinded phase (n = 136 in the Solesta group and n = 70 in the Sham group), treatment-emergent adverse events were experienced by 72% of the Solesta-treated patients and 60% of Sham-treated patients. Table 3 provides an overview of treatment-emergent adverse events during the 6-month blinded phase.

Table 3: Overview of Adverse Events during the 6-Month Blinded Phase of the Pivotal Study

	Solesta (n = 136) n (%)	**Sham (n = 70) n (%)**
Any treatment-emergent adverse event	98 (72.1)	42 (60.0)
Severe treatment-emergent adverse events	6 (4.4)	1 (1.4)
Serious treatment-emergent adverse events	7 (5.1)	2 (2.9)
Treatment-emergent adverse events considered related to study treatment by the investigator (treatment-related adverse events)	66 (48.5)	19 (27.1)
Serious treatment-related adverse events[a]	2 (1.5)	0

[a]Serious treatment-related adverse events were one case of *E.coli* bacteremia and one case of rectal abscess. A third patient experienced a serious treatment-related adverse event of rectal abscess during the open phase.

Safety data for Solesta are available from 359 treatments in 197 total patients followed for up to 36 months post treatment during the blinded and open phases of the Pivotal Study (i.e., the long-term population, including 136 patients who received Solesta during the blinded phase and an additional 61 patients who received Solesta during the open phase). Greater than 80% of subjects had two injections with Solesta (initial treatment and re-treatment approximately 1 month later); 113 of 136 patients (83.1%) received two Solesta injections during the blinded phase and 49 of 61 patients (80.3%) received two Solesta injections during the open phase. At least one treatment-emergent adverse event was experienced by 87% of patients in the long-term population. Severe treatment-emergent adverse events were reported for 12% of patients. For the subgroup of 61 patients who received Solesta at the start of the open phase, treatment-emergent AEs were experienced by 85% of patients and severe treatment-emergent adverse events were reported for 12% of patients.

In the long-term population, treatment-related adverse events (i.e., treatment-emergent adverse events considered by the investigator to be related to Solesta injection) were experienced by 104 of 197 patients (53%) up to 36 months after treatment. For the subgroup of 61 patients who received Solesta at the start of the open phase, 31 of 61 (51%) had treatment-related adverse events during follow-up. Three of 197 patients (1.5%) had treatment-related adverse events that were deemed serious by the investigators. These serious treatment-related adverse events included one subject with *E.coli* bacteremia who presented with an ongoing urinary tract infection, prostatic hypertrophy, and possible upper respiratory tract infection, and two subjects with rectal abscess. The event of *E. coli* bacteremia and one event of rectal abscess occurred during the blinded phase; the other event of rectal abscess occurred during the open phase. These serious treatment-related adverse events resolved following treatment without sequelae within 35 days of event onset. The times from injection to event onset and other details of the three serious treatment-related adverse events are shown in Table 4.

Table 4: Serious Treatment-Related Adverse Events during the Blinded or Open Phases (Up to 36 Months Post Treatment)

Event	Treatment Group	Intensity	Time from Injection to Event Onset	Event Duration	Outcome
Escherichia coli bacteremia[a]	Solesta treatment - blinded phase	Moderate	0.5 days post first injection	35 days	Recovered
Rectal abscess[a]	Solesta treatment - blinded phase	Mild	2 days post second injection	5 days	Recovered
Rectal abscess[b]	Solesta treatment - open phase	Severe	4.5 months post second injection	5 days	Recovered

[a]These events occurred during the blinded phase.
[b]This event occurred during the open phase.

Overall, 96% of treatment-related adverse events required no intervention or required medical or simple non-invasive interventions, including application of local pressure, silicone ointment, water irrigation, and warm baths. Ten treatment-related adverse events required more invasive procedures, as follows (with time from injection to event onset in parentheses): six cases of perianal drainage or incision and drainage of abscesses (2, 3, 15, 140, 1000, and 1053 days post injection, respectively), one case of lancing of a hemorrhoid (1 day post injection), one case of a Kenalog injection in a pre-existing anal scar (255 days post injection), one case of rubber band ligation of an anal prolapse (288 days post injection), and one case of rectovaginal cyst removal (594 days post injection). These events requiring intervention were considered by the investigator to be moderate or mild, with the exception of one severe case (nonserious) of rectal abscess (event onset 3 days after injection) that required drainage.

As shown in Table 5, the most frequent treatment-related adverse events following Solesta treatment pertained to post-treatment proctalgia, minor anal or rectal bleeding, post-treatment fever, abdominal complaints (such as diarrhea and constipation), and events potentially related to peri-operative infection. Most of these treatment-related adverse events were experienced soon after injection with Solesta; the highest incidence occurred during the 48-hour interval following the first injection. The onset of treatment-related adverse events, such as proctalgia, were also relatively frequent from > 1 month to 2 months post first injection; this result is consistent with re-injection of study treatment for most patients at 1 month post first injection (161 of 197 patients received a second injection at 1 month) in the Pivotal Study. All of the events shown in Table 5 resolved during follow-up with the exception of one mild event of injection site nodule that was considered chronic/stable.

Table 5: Related Adverse Events (Including Serious AEs) by Time Interval of Event Onset Experienced by at Least Two Patients Following Blinded or Open-Label Treatment with Solesta through Month 36 in the Pivotal Study MedDRA Preferred Term. Safety Population (n=197)

	↓ 1st Solesta injection		↓ 2nd Solesta injection (at 1 month)				
MedDRA Preferred Term	**1st Solesta injection - 48 hours (N = 197) n (%)**	**>48 hours - 7 days (N = 197) n (%)**	**>7 days - 1 month (N = 197) n (%)**	**>1 month -2 months (N = 197) n (%)**	**>2 months - 6 months (N = 197) n (%)**	**>6 months - 36 months (N = 194) n (%)**	**>36 months (N = 117) n (%)**
Proctalgia	17 (8.6%)	2 (1.0%)	7 (3.6%)	12 (6.1%)	1 (0.5%)	3 (1.5%)	0
Injection site hemorrhage	5 (2.5%)	0	3 (1.5%)	6 (3.0%)	3 (1.5%)	0	0
Rectal hemorrhage	2 (1.0%)	1 (0.5%)	2 (1.0%)	6 (3.0%)	2 (1.0%)	2 (1.0%)	0
Pyrexia	7 (3.6%)	0	2 (1.0%)	5 (2.5%)	0	0	0
Diarrhea	0	1 (0.5%)	3 (1.5%)	3 (1.5%)	1 (0.5%)	2 (1.0%)	0
Injection site pain	6 (3.0%)	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
Anorectal discomfort	3 (1.5%)	0	2 (1.0%)	2 (1.0%)	2 (1.0%)	0	0
Anal hemorrhage	4 (2.0%)	0	1 (0.5%)	3 (1.5%)	1 (0.5%)	0	0
Rectal discharge	2 (1.0%)	0	1 (0.5%)	4 (2.0%)	0	0	0
Proctitis	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	0	0
Anal prolapse	0	0	0	0	1 (0.5%)	2 (1.0%)	0
Constipation	0	0	0	2 (1.0%)	1 (0.5%)	0	0
Anal pruritus	0	0	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	0
Abdominal pain lower	1 (0.5%)	0	0	0	1 (0.5%)	0	0
Defecation urgency	0	0	0	2 (1.0%)	0	0	0
Painful defecation	1 (0.5%)	0	0	1 (0.5%)	0	0	0
Rectal obstruction	1 (0.5%)	0	0	0	1 (0.5%)	0	0
Chills	3 (1.5%)	0	1 (0.5%)	0	0	0	0
Injection site nodule	0	0	0	0	0	3 (1.5%)	0
Pain	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Rectal abscess	1 (0.5%)	0	1 (0.5%)	1 (0.5%)	0	0	0
Anal fissure	0	0	0	1 (0.5%)	0	1 (0.5%)	0
Rectovaginal septum abscess	0	0	0	0	0	1 (0.5%)	1 (0.9%)
Dyspareunia	0	0	0	0	2 (1.0%)	0	0
Alopecia	0	0	0	1 (0.5%)	1 (0.5%)	0	0

Notes: The following treatment-related adverse events were reported for one patient each: abdominal discomfort, abdominal distension, abdominal pain, abdominal rigidity, FI, hard feces, gastrointestinal motility disorder, gastrointestinal pain, hemorrhoids, intestinal mass, nausea, rectal spasm, device dislocation, fatigue, implant site cyst, injection site inflammation, injection site irritation, injection site swelling, pelvic mass, anal abscess, *Escherichia coli* bacteremia, injection site pustule, mucosal excoriation, c-reactive protein increased, back pain, musculoskeletal pain, urinary retention, genital prolapse, perineal pain, vaginal discharge, vulvovaginal pain, cold sweat, and dermatitis. The down arrow symbol (↓) indicates the timing of Solesta injections. Greater than 80% of subjects had two injections with Solesta (initial treatment and re-treatment approximately 1 month later).

Combined with the supportive studies, a total of 346 patients received 566 treatments with Solesta. All three studies utilized similar inclusion/exclusion criteria and all three studies used exactly the same procedure for administering Solesta. The multi-center Open-Label Study demonstrated similar safety results as the Pivotal Study. A total of 163 AEs were reported by 71 of the 115 patients treated with Solesta in the Open-Label Study. Of these AEs, 79 AEs reported by 44 patients (38%) were assessed by the investigators to be related to the study treatment. Thus, the incidence of treatment-related AEs per total number of per-formed treatments was 51.3% (79 events/154 treatments). Similar to the Pivotal Study, the five most frequently reported types of treatment-related AEs were proctalgia, pyrexia, constipation, diarrhea, and injection site pain. Six treatment-related AEs reported in four patients were classified as serious in the study. Three of these serious and treatment-related adverse events were cases of abscess reported by three patients and the remaining three were reported by a single patient who had a rectal prolapse with concurrent rectal bleeding and pain. In this latter case, tissues surrounding a Solesta bulge had prolapsed downwards in the anal canal and the Solesta bulge was excised in surgery.

In the Proof-of-Concept Study, 34 patients were treated in the study and 33 patients were followed for 24 months. In total, 53 treatments with Solesta were administered in the study. These patients experienced a total of 86 treatment-related adverse events that were reported by 29 patients. No treatment-related adverse event was reported as serious. The duration was 1-4 days for most events and all events were resolved within one week. No adverse events occurred after month 12. One patient gave birth to a healthy child approximately 18 months after treatment and the delivery was a normal vaginal delivery. The observed adverse events were similar to those seen in the Pivotal Study.

Effectiveness

Primary Efficacy Objective - Pivotal Study

The Pivotal Study included a primary efficacy objective composed of three parts. All three parts of the primary objective were met. The study was only powered for the primary endpoint and was not designed or powered to demonstrate a statistical difference between Solesta and Sham for the secondary efficacy endpoints.

Superiority was shown for Solesta (53.2%) versus Sham (30.7%) at 6 months (p=0.004; logistic regression), as illustrated in Figure 1, based on analysis of proportion Responder$_{50}$. Responder$_{50}$, defined as proportion of patients with a ≥ 50% reduction in number of incontinence episodes compared to baseline, has been used to objectively evaluate response to treatments for FI in other studies.

The second success criterion required that the results achieve a pre-specified minimum level of responders in the treatment group as defined by a lower confidence limit (LCL) of at least 35%. The LCL of the 95% confidence interval of the proportion Responder$_{50}$ at 6 months was 40.2%, as illustrated in Figure 2.

Figure 1. Comparison of Proportion Responder$_{50}$ at 6 Months

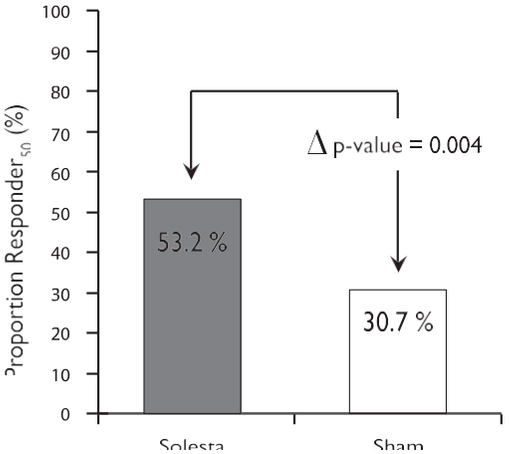
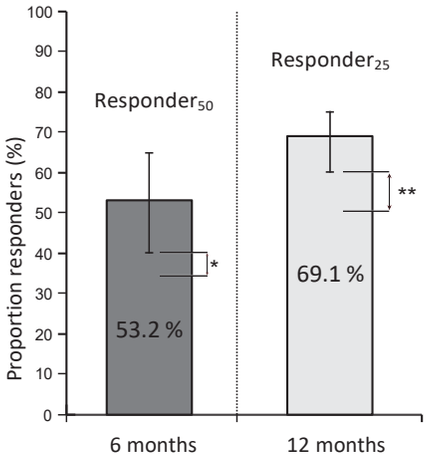


Figure 2. Solesta Proportion Responders at 6 and 12 Months



* Responder$_{50}$ LCL = 40.2 % > 35 %
** Responder$_{25}$ LCL = 61.4 % > 50 %

The third success criterion concerned durability of the treatment effect and required a minimum level of proportion Responder$_{25}$ (≥ 25% improvement from baseline) for Solesta at 12 months, as defined by a lower confidence limit of 50%. The LCL for proportion Responder$_{25}$ at 12 months was 61.4%, as illustrated in Figure 2.

As an additional supporting analysis, the proportion Responder$_{50}$ at 12 months after last treatment was also calculated and it was 57.4%, similar to the results at 6 months. Analyses were performed to determine whether there was any association between baseline or demographic characteristics and treatment response. No such relationship was found.

Primary Endpoint Pivotal and Supporting Studies

All three studies show durability of the treatment effect to 24 months as evidenced by the proportion Responder$_{50}$. As shown in Table 6, the proportion Responder$_{50}$ at 6, 12, and 24 months were similar across all three studies. In addition, the Pivotal Study showed durability of the treatment effect to 36 months.

Table 6: Summary of Proportion of Responder$_{50}$ at 6,12, 24, and 36 Months with Solesta Treatment

Proportion Responder$_{50}$ [95% CI]	Pivotal Study (ITT, PIM [6 month time point]; ITT, LOCF [12, 24, and 36 month time points])[a]	Open-Label Study (ITT, OC)	Proof-of-Concept Study (OC)
6 months	53.2% [40.2–65.8] n= 136	57.1% [47.3–66.9] n=98	44.1% [27.4–60.8] n=34
12 months	57.4% [49.0–65.7] n=136	64.4% [54.3–74.4] n=87	55.9% [39.2–72.6] n=34
24 months	54.4% [46.0-62.8] n = 136	62.7% [51.7-73.6] n=75	59.4% [42.4–76.4] n=32
36 months	52.2% [43.8-60.6] n=136	N/A	N/A

[a]The responder$_{50}$ proportion at 6 months in the ITT population was determined from the primary imputation model and is the same as shown in Figure 1. The responder$_{50}$ proportions at 12, 24, and 36 months in the ITT population were determined by the LOCF method. The responder$_{50}$ proportion at 6 months by the LOCF method was 52.2% [43.8-60.6].
CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; PIM = primary imputation model; OC = observed cases; n = number of patients

Secondary Endpoints for Pivotal and Supporting Studies

The following secondary endpoints were evaluated in the three clinical studies:

- FI episodes
- FI-free days
- FIQL assessment
- CCFIS or Miller Score

Fecal Incontinence Episodes

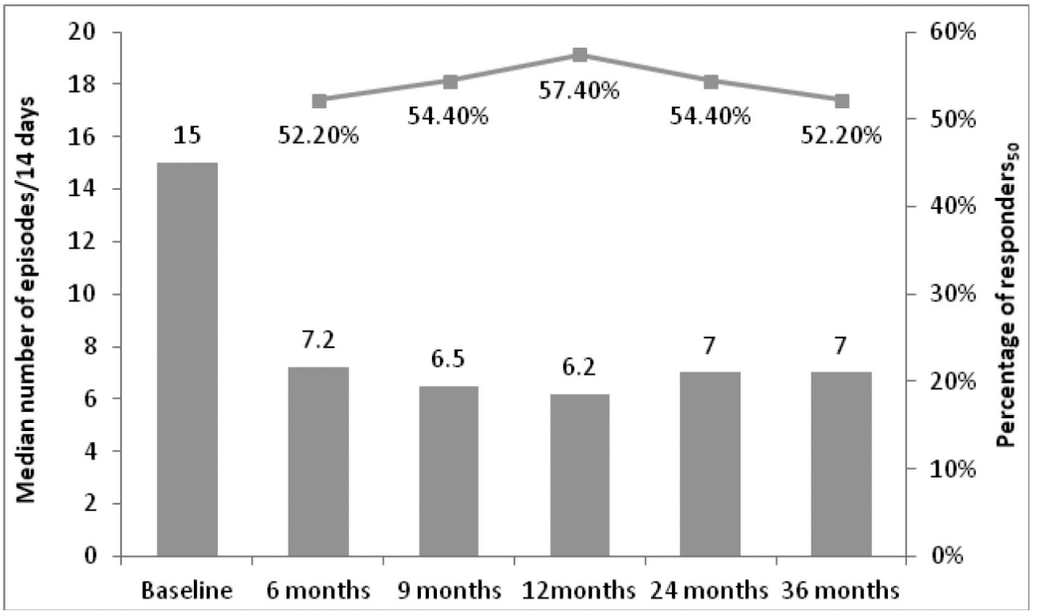
In the Pivotal Study, reductions in number of FI episodes from baseline at both 3 and 6 months were observed in both the Solesta and Sham treatment groups. For the Solesta group, the median FI episodes were shown to decrease from 15 episodes at baseline to 7.2 episodes at 6 months and 6.2 episodes at 12 months. For the Sham group, the median FI episodes were shown to decrease from 12.5 episodes at baseline to 10.0 episodes at 6 months (see Table 7). Both the Solesta and Sham groups showed a change from baseline at 6 months, and the change from baseline in the Solesta group was larger than that observed for the Sham group. Similar reductions from baseline with Solesta treatment were observed in the Open-Label Study and the Proof-of-Concept Study.

Table 7: Median Number of Fecal Incontinence Episodes/14 Days for Each Treatment Group and Change from Baseline to 6 Months. As Observed. Last Observation Carried Forward (LOCF). ITT population (n=206 patients: Pivotal Study)

Number of Episodes	Solesta (n=136) Median	Sham (n=70) Median	Difference in Median Changes Between Groups (Solesta-Sham)
Baseline	15.0	12.5	
6 months	7.2	10.0	
Δ from baseline	-6.0	-3.0	-3.0
% Δ from baseline	-50.6	-22.6	-28.0

Figure 3 shows the sustained improvement in Responder$_{50}$ analysis and reduction in FI episodes over 36 months in the Pivotal Study for the Solesta group only. After 6 months, patients in the Sham treatment group were offered active treatment and were excluded from further analysis.

Figure 3. Median Number of FI Episodes and Proportion Responder$_{50}$ at Each Follow Up Time Point in the Pivotal Study. Solesta ITT Population (n=136)



FI-Free days

In all three studies, an increase in number of FI-free days was observed with Solesta treatment. In the Pivotal Study at 6 months, both the Solesta and Sham treatment groups experienced an increase in number of FI-free days from their pre-treatment baseline values of 4.4 days and 4.8 days, respectively. However, the Solesta group demonstrated an increase of 3.1 FI-free days when compared to the Sham group increase of 2.0 days. At 12 months, the increase in number of FI-free days in the Solesta group was maintained at 3.4 days. Similar increases in number of FI-free days with Solesta treatment were shown in the Open-Label Study and the Proof-of-Concept Study.

Fecal Incontinence Quality of Life Scale (FIQL)

The FIQL is a validated tool that is specifically designed to assess the impact of FI on a patient's quality of life. In the blinded phase of the Pivotal Study, improvement in FIQL scores compared to baseline was observed in both the Solesta and Sham groups at 6 months. The change from baseline score was greater in the Solesta group than the Sham group in all four domains: Lifestyle (Δ=0.22), Coping/Behavior (Δ=0.25), Depression/Self-Perception (Δ=0.09) and Embarrassment domains (Δ=0.16) (see Table 8). In the Open-Label Study, FIQL scores showed a similar improvement. The Proof-of-Concept Study did not evaluate FIQL

Cleveland Clinic Florida Incontinence Score (CCFIS)
The CCFIS is a validated measure of the impact of FI on patients. In the Pivotal Study, for both the Solesta and Sham groups, CCFIS responses were used to objectively evaluate response treatment comparing baseline to 6 months.

The second success criterion required FI improvement to achieve a pre-specified minimum level of response in the treatment group as compared to the Sham group, baseline to 6 months. The difference at 6 months in mean change from baseline between the Solesta group and the Sham group was small (see Table 8). Solesta showed improvements from baseline at 12 months in both the Pivotal Study and the Open-Label Study.

The Proof-of-Concept Study did not incorporate CCFIS but instead used the Miller Score, another assessment tool for FI. The Miller Score is based on a subject interview using standardized questions regarding incidence and type of incontinence (solid, liquid, or gas). Improvements from baseline and sustained improvements were shown at 6, 12, and 24 months.

Table 8: Secondary Efficacy Evaluations of Difference in Change from Baseline Between Solesta and Sham at 6 Months. LOCF. ITT Population (n=206 Patients: Pivotal Study)

Secondary Endpoints	Score/Scale Range	Estimate of Mean Change from Baseline		Estimate of Difference (95% CI)
		Solesta	Sham	
Fecal Incontinence Quality of Life Scale (FIQL) (higher score = increased QoL)				
Lifestyle*	1-4	0.33	0.11	0.22 (0.04:0.40)
Coping/Behavior*	1-4	0.44	0.19	0.25 (0.08:0.43)
Depression/Self-Perception*	1-6	0.27	0.18	0.09 (-0.08:0.26)
Embarrassment*	1-4	0.53	0.38	0.16 (-0.05:0.36)
Cleveland Clinic Florida Incontinence Score (CCFIS)				
CCFIS score†	0 = continent; 20 = total incontinence	-3.06	-2.85	-0.21 (-1.15:0.72)

* Positive value indicates improvement; † Negative value indicate improvement

Post-Approval Study Results

Summary of the Post-Approval Study Methods
The safety and effectiveness of Solesta were studied in a prospective, single-arm, multicenter, observational post-approval study with a 36-month follow-up after the last Solesta treatment. The study allowed subjects to receive a second Solesta treatment 1 to 3 months after the first treatment, if needed. Thus, subjects that received a second Solesta treatment were followed for 39 months. The first subject was enrolled on May 31, 2012, and the last subject completed follow-up by June 1, 2019. A total of 283 subjects were enrolled in the study.

Study Objective
The purpose of the Post-Approval Study was to evaluate the safety and effectiveness of the Solesta Injectable Bulking Agent in the treatment of FI through 3 years in a real-world setting.

Study Design
The Post-Approval Study was a prospective, single-arm, multicenter, observational clinical study. The Post-Approval Study was a condition of PMA approval.

Study Population
To be eligible for enrollment in the study, subjects had to be at least 18 years old, have FI, have failed conservative therapy (e.g., diet, fiber therapy, medications that treat diarrhea), and were scheduled to receive Solesta treatment. Subjects with an active inflammatory bowel disease, an immunodeficiency disorder or ongoing immunosuppressive therapy, previous radiation treatment to the pelvic area, significant mucosal or full thickness rectal prolapse, active anorectal conditions including abscess, fissures, sepsis, bleeding, proctitis, or other infections, anorectal atresia, tumors, stenosis or malformation, a rectocele, rectal varices or an existing implant for FI including Solesta, artificial bowel sphincter, or sacral nerve stimulator were excluded.

Demographic and baseline characteristics of the subjects are listed in Table 9 and Table 10, respectively.

Table 9: Summary of Demographic Data

Outcome	Options	Subjects
Age	Mean (SD) (Min, Median, Max) N	64.6 (12.99) (23, 66, 95) N= 283
Age group	< 65 Years	129 (45.6%)
	≥ 65 Years	154 (54.4%)
BMI	Mean (SD) (Min, Median, Max) N	27.8 (7.72) (17, 26, 96) N= 279
Ethnicity	Hispanic or Latino	15 (5.3%)
N (%)	Not Hispanic or Latino	268 (94.7%)
Race	American Indian/Alaskan	3 (1.1%)
N (%)	Asian	4 (1.4%)
	Black/African American	16 (5.7%)
	White	259 (91.8%)
Gender	Female	242 (85.5%)
N (%)	Male	41 (14.5%)

Table 10: Summary of Baseline Data, ITT

Outcome	Options	Subjects (%)
Etiology	Congenital abnormality	1 (0.4%)
N (%)	Iatrogenic	20 (7.1%)
	Neurogenic	26 (9.2%)
	Obstetric	154 (54.4%)
	Other	82 (29.0%)
Prior FI surgery	No	250 (88.3%)
N (%)	Yes	33 (11.7%)
Prior biofeedback/	No	120 (42.4%)
Sphincter exercise N (%)	Yes	163 (57.6%)
FI duration	12 Months - 5 Years	135 (47.7%)
N (%)	< 12 Months	21 (7.4%)
	> 5 Years	127 (44.9%)
Urinary incontinence	No	169 (59.7%)
N (%)	Yes	114 (40.3%)
Anti-diarrheal meds used	No	111 (39.2%)
N (%)	Yes	172 (60.8%)
Pre-menopausal	Females: No	179 (74.0%)
N (%)	Females: Yes	63 (26.0%)
High BP	No	107 (37.8%)
N (%)	Yes	176 (62.2%)
Diabetes	No	257 (90.8%)
N (%)	Yes	26 (9.2%)

Data Source

Data were prospectively collected at 18 sites in the United States.

Key Study Endpoints

The primary safety endpoint was the occurrence of device-related AEs at 3, 6, 12, 24, and 36 months after the last Solesta treatment. The secondary safety endpoint was device-related infectious AEs reported during the peri-injection interval in subjects treated with and without prophylactic antibiotics prior to injection.

The primary effectiveness endpoint was freedom from FI re-intervention (or lack of occurrence) of FI re-intervention ≥ 3 months after the last primary Solesta treatment. The secondary effectiveness endpoints, assessed at 3, 6, 12, 24, and 36 months after the last Solesta treatment, were FIQL, CCFIS, a patient global assessment of improvement, Global Perceived Effect (GPE) score, and time to FI re-intervention.

The primary performance endpoint was an evaluation of the anatomic stability of Solesta using transrectal ultrasounds obtained 3, 6, and 36 months after the last Solesta treatment in a sub-study of 58 subjects at six sites. The secondary performance endpoints were the presence or absence of implants and any local shift in the implant(s) at 6 and 36 months after the last Solesta treatment.

Total Number of Enrolled Study Sites and Subjects

As shown in Table 11, a total of 283 subjects were enrolled in the intent-to-treat (ITT) population and 186 subjects (73.5%) were evaluated at the final visit (36 months). The per protocol (PP) population, which consisted of subjects with complete primary effectiveness data and no major protocol deviations, included 134 subjects. Additionally, a subset of 58 subjects in the ITT population were included in a sub-study to evaluate the performance endpoints. There were eight deaths, none of which were device-related, and 22 withdrawals reported during the study.

Table 11: Subject Accountability, ITT Population

	Baseline	3 Months	6 Months	12 Months	24 Months	36 Months
Theoretical[1]	283	283	283	283	283	283
Deaths[2]	0	0	2	5	5	8
Withdrawals[3]	0	1	4	11	16	22
Expected[4]	283	282	277	267	262	253
Actual A[5]	-	250	227	214	188	186
Actual B[6]	283	250	227	214	188	186
%Follow-up A[7]	-	88.7%	81.9%	80.1%	71.8%	73.5%
%Follow-up B[8]	100%	88.7%	81.9%	80.1%	71.8%	73.5%

[1] Number of subjects that reached the beginning of the study window associated with each visit.
[2] Cumulative number of subjects that died during or prior to the study visit.
[3] Cumulative number of subjects that were withdrawn during or prior to the study visit.
[4] Theoretical subjects minus the number of deaths or withdrawals.
[5] Subjects with primary endpoint data (FI evaluation) at the relevant visit.
[6] Subjects who returned to the office with any data at the relevant visit.
[7] Actual A/Expected *100
[8] ActualB/Expected *100

Study Visits and Length of Follow-Up

Patients were screened for eligibility and baseline information was collected prior to Solesta treatment. All subjects received a Solesta treatment. Subjects had the option of a second treatment between 1 and 3 months after the first treatment. Subjects were followed at 3, 6, 12, 24, and 36 months after their last Solesta treatment.

Summary of the Post-Approval Study Results

The primary safety endpoint was measured by device-related AEs that occurred during the injection, peri-injection, and long-term intervals through 36 months after the last Solesta treatment. Overall, 43 (15.2%) subjects in the study reported device-related AEs. None were serious, most were mild, most were gastrointestinal disorders, and most resolved quickly.

The secondary safety endpoint was the device-related infectious AEs reported during the peri-injection interval in subjects treated with and without prophylactic antibiotics prior to injection. Only one subject (0.4%), who had two treatments and was not treated with prophylactic antibiotics, experienced one peri-injection device-related infectious AE, vaginitis bacterial. This AE was mild, procedure-related, and resolved with additional treatment.

There were no SAEs or deaths that were device or injection-related. AEs related to the injection were reported in 68 (24.0%) subjects in the study. None were serious, most were mild, most were gastrointestinal disorders, and most resolved quickly. No new or unexpected safety findings were identified. All of the reported AEs were consistent with the established safety profile of Solesta.

At 36 months, 152 subjects were free from FI re-intervention (primary effectiveness endpoint) and 40 were not. Based on Bayesian analysis, the primary effectiveness objective was met, and study success was achieved. The sensitivity and subgroup analyses supported the robustness of the primary effectiveness results and the study success finding.

All FIQL domains (Lifestyle, Coping/Behavior, Depression/Self-Perception and Embarrassment) showed improvement over baseline at all post-treatment visits in subjects, regardless of the number of treatments.

The mean change from baseline in the CCFIS score was -4.0 at 36 months after the last Solesta treatment. The CCFIS subscale (Gas, Lifestyle, Liquid, Solid, and Wears Pad) rates for Always and Usually decreased from baseline at 36 months. Thus, the CCFIS score and all of the CCFIS subscales showed symptom relief following Solesta treatment.

From baseline to 36 months after the last Solesta treatment, the improvement in each domain of the FIQL (Lifestyle, Coping/Behavior, Depression/Self-Perception and Embarrassment) and the reduction in symptoms burden based on the CCFIS scale were statistically and clinically significant.

For GPE, 53.8% of all subjects reported much improvement (Significantly or Moderately Relieved) in the degree of FI and 72.6% reported some improvement (Significantly, Moderately, and A Little Bit Relieved).

The available ultrasound data at the 6- and 36-month visits support that the Solesta implants remain present and, in general, do not shift from one anatomic position to another. Furthermore, this finding is supported by the low rate of FI re-interventions, which indicates that the device continued to perform as indicated.

The primary effectiveness endpoint of freedom from FI re-intervention was met, and study success was achieved. The sensitivity and subgroup analyses support the robustness of the primary effectiveness analysis. The secondary effectiveness quality of life endpoints consistently showed symptom relief after Solesta treatment. Thus, the study results confirmed the benefits of Solesta treatment. The available performance data at the 6- and 36-month visits support that the Solesta implants remain present and, in general, do not shift from one anatomic position to another. Further, no new or unexpected safety findings were identified. All of the reported AEs are consistent with the established safety profile of Solesta; therefore, the clinical evidence from this post-approval study show that the benefits outweigh the risks and support the safety and effectiveness finding of the Solesta PMA.

Final Safety Findings

The primary safety endpoint was measured by device-related AEs that occurred during the injection, peri-injection, and long-term intervals through 36 months after the last Solesta treatment. Overall, 43 (15.2%) subjects in the study reported device-related AEs. None were serious, most were mild, most were gastrointestinal disorders, and most resolved quickly. The device related AEs are listed by interval in Table 12.

Table 12: Device Related AEs by Interval, Safety/ITT Population

Body System	Type of AE	Injection[1] Subjects (%)	Peri-Injection[2] Subjects (%)	Long-Term[3] Subjects (%)
Gastrointestinal disorders	Abdominal pain	2/ 283 (0.7%)	-	1/ 283 (0.4%)
	Abnormal feces	1/ 283 (0.4%)	-	-
	Anal pruritus	1/ 283 (0.4%)	-	-
	Anorectal discomfort	10/283 (3.5%)	-	3/ 283 (1.1%)
	Constipation	1/ 283 (0.4%)	1/ 283 (0.4%)	1/ 283 (0.4%)
	Diarrhea	2/ 283 (0.7%)	-	2/ 283 (0.7%)
	Hematochezia	1/ 283 (0.4%)	1/ 283 (0.4%)	-
	Proctalgia	12/283 (4.2%)	1/ 283 (0.4%)	5/ 283 (1.8%)
	Rectal discharge	1/ 283 (0.4%)	-	1/ 283 (0.4%)
	Rectal hemorrhage	1/ 283 (0.4%)	2/ 283 (0.7%)	5/ 283 (1.8%)
	Hemorrhoids	-	1/ 283 (0.4%)	-
	Rectal tenesmus	-	1/ 283 (0.4%)	-
General disorders and administration site conditions	Chills	1/ 283 (0.4%)	-	1/ 283 (0.4%)
	Implant site effusion	2/ 283 (0.7%)	-	1/ 283 (0.4%)
	Injection site discomfort	2/ 283 (0.7%)	-	-
	Pyrexia	1/ 283 (0.4%)	-	-
	Mucosal induration	-	1/ 283 (0.4%)	-
Infections and infestations	Vulvovaginal mycotic infection	1/ 283 (0.4%)	-	-
	Vaginitis bacterial	-	1/ 283 (0.4%)	-
	Perirectal abscess	-	-	1/ 283 (0.4%)
Musculoskeletal and connective tissue disorders	Pain in extremity	1/ 283 (0.4%)	-	-
Renal and urinary disorders	Urinary hesitation	2/ 283 (0.7%)	-	1/ 283 (0.4%)
	Urinary retention	1/ 283 (0.4%)	-	1/ 283 (0.4 %)
	Urethral pain	-	1/ 283 (0.4%)	-
	Hematuria	-	-	1/ 283 (0.4%)
	Micturition urgency	-	-	1/ 283 (0.4%)
Neoplasms benign, malignant and unspecified	Vaginal neoplasm	-	-	1/ 283 (0.4%)
Nervous system disorders	Headache	-	-	1/ 283 (0.4%)
Reproductive system and breast disorders	Hematospermia	-	-	1/ 283 (0.4%)
	Prostatitis	-	-	1/ 283 (0.4%)
Vascular disorders	Hematoma	-	1/ 283 (0.4%)	-
	Bloody discharge	-	-	1/ 283 (0.4%)
	Thrombosis	-	-	1/ 283 (0.4%)

[1] ≤ 2 days following first Solesta injection
[2] > 2 days to ≤ 2 weeks following first Solesta injection
[3] > 2 weeks following first Solesta injection

The secondary safety endpoint was device-related infectious AEs reported during the peri-injection interval in subjects treated with and without prophylactic antibiotics prior to injection. Only one subject (0.4%), who had two treatments and was not treated with prophylactic antibiotics, experienced one peri-injection device-related infectious AE, vaginitis bacterial. This AE was mild, procedure-related and resolved with additional treatment.

AEs related to the injection were reported in 68 (24.0%) subjects in the study. None were serious, most were mild, most were gastrointestinal disorders, and most resolved quickly.

There were no SAEs or deaths that were device- or injection-related. No new or unexpected safety findings were identified. All of the reported AEs are consistent with the established safety profile of Solesta.

Final Effectiveness Findings

The primary effectiveness endpoint was freedom from FI re-intervention. Re-intervention for FI included any of the following FI treatments: sphincteroplasty, implantation of artificial bowel sphincter, retreatment with Solesta, graciloplasty, SNS or other surgical interventions. Subjects were evaluated at 3, 6, 12, 24, and 36 months after the last Solesta treatment for the occurrence (or lack of occurrence) of FI re-intervention ≥ 3 months after the last primary Solesta treatment.

Table 13 summarizes the number of subjects and their re-intervention status evaluated at 3, 6, 12, 24, and 36 months after last Solesta treatment. The re-intervention rate is cumulative. At 36 months, 152 subjects were free from FI re-intervention and 40 were not.

Table 13: Summary of Re-Intervention Status by Time Point, ITT Population

	3 Months	6 Months	12 Months	24 Months	36 Months
Subjects withdrawn	14	41	60	77	91
Subjects followed up	269	242	223	206	192
Subjects without re-intervention	267	231	206	172	152
Subjects with re-intervention	2	11	17	34	40

Study success was defined as a FI re-intervention rate less than 50% through 36 months. Bayesian statistics were performed and, as shown in Table 14, the primary effectiveness objective was met, and study success was achieved.

Table 14: Summary of Posterior Distribution of Re-intervention Rate through 36 Months, ITT Population

Summary	Value
P (Rate of re-intervention through 36 months < 50%)	1.000
Mean	0.189
St Dev	0.027
Lower 95% credible interval	0.140
Upper 95% credible interval[1]	0.244

[1] Study success defined as < 0.5

Four sensitivity analyses were performed:
1) No Bayesian imputation;
2) Controlling for covariates;
3) Tipping point; and
4) Surgical FI re-interventions only.

Additionally, the Bayesian primary analysis was performed on three different subgroups:
1) Per protocol population;
2) Subjects with one treatment; and
3) Subjects with two treatments.

All of the sensitivity and subgroup analyses supported the robustness of the primary effectiveness results and the study success finding.

The secondary effectiveness endpoints were:
1) FIQL,
2) CCFIS,
3) GPE Score, and
4) Time to FI re-intervention.

All FIQL domains (Lifestyle, Coping/Behavior, Depression/Self-Perception, and Embarrassment) showed improvement over baseline at all post-treatment visits in subjects, regardless of the number of treatments.

The change from baseline in FIQL domains at 36 months for the ITT Population is presented for all subjects in Table 15.

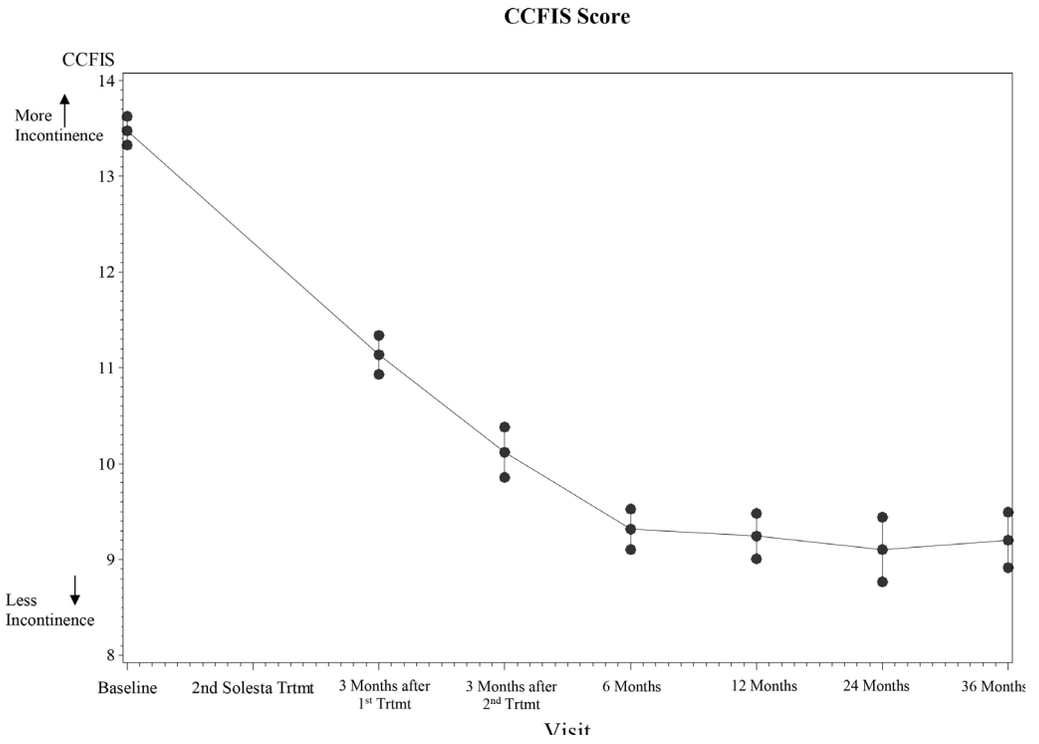
Table 15: FIQL Domains Change from Baseline, ITT Population (N=154)

Visit	Lifestyle Subjects (SD)	Coping/Behavior Subjects (SD)	Depression/Self-Perception Subjects (SD)	Embarrassment Subjects (SD)
36 Months	0.5 (0.77)	0.7 (0.84)	0.4 (0.69)	0.8 (0.92)

CCFIS scores were collected at baseline, 3, 6, 12, and 36 months after the last Solesta treatment. The CCFIS is a summed score of five individual parameters (i.e., frequency of incontinence to gas, liquid stool leakage, solid stool leakage, of need to wear pad, and of lifestyle changes) each of which is scored on a scale from 0 (absent) to 4 (daily). A summed score of 0 represents complete control while a score of 20 represents complete incontinence.

The mean change from baseline in the CCFIS score was -4.0 at 36 months after last Solesta treatment. A graphical representation of the CCFIS score by visit for all subjects in the ITT population is presented in Figure 4.

Figure 4: CCFIS Score by Visit



The CCFIS subscale (Gas, Lifestyle, Liquid, Solid, and Wears Pad) rates for Always and Usually decreased from baseline at 36 months. Thus, the CCFIS score and all of the CCFIS subscales showed symptom relief following Solesta treatment.

From baseline to 36 months after the last Solesta treatment, the improvement in each domain of the FIQL (Lifestyle, Coping/ Behavior, Depression/Self-Perception and Embarrassment) and the reduction in symptoms burden based on the CCFIS were statistically significant. Furthermore, for CCFIS and each FIQL sub-scale, the mean change from baseline to 36 months post treatment exceeds the minimal clinically important difference (MCID), and therefore, is considered to be clinically significant as well.

The GPE Score, a global assessment of improvement, was collected at 6, 12, and 36 months after the last Solesta treatment. Subjects were asked to select the one response that best describes how their FI condition at the time of the visit, compared to how it was before the Solesta treatment. The GPE score ranges from 1 to 7 points, where a score of 1 or 2 indicates much improvement, while a score 6 or 7 indicates much worsening. For all subjects at all visits, from 45% to 64% of the subjects reported much improvement (Significantly or Moderately Relieved) in the degree of FI and from 73% to 87% reported some improvement (Significantly, Moderately and A Little Bit Relieved).

Freedom from FI re-intervention was estimated by the Kaplan-Meier method, along with the corresponding 95% confidence intervals. The KM survival rate is estimated to be 82% at 36 months.

The primary performance endpoint was an evaluation of the anatomic stability of Solesta using transrectal ultrasounds obtained 3, 6, and 36 months after the last Solesta treatment in a sub-study of 58 subjects at six sites. The secondary performance endpoints were the presence or absence of implants and any local shift in the implant(s) at 6 and 36 months after the last Solesta treatment. Although technical difficulties with the ultrasound scans resulted in lower evaluable data than originally expected, the available data at the 6- and 36-month visits support that the Solesta implants remain present and, in general, do not shift from one anatomic position to another. Furthermore, this finding is supported by the low rate of FI re-interventions, which indicates that the device continued to perform as indicated.

Study Strengths and Limitations

The strengths of this study are the large number of subjects treated with one or two Solesta treatments, the follow-up period of 36 months, the use of two health-related quality of life instruments, assessment of clinical significance of quality-of-life scores based on an analysis to determine the MCID for the scores, and the consistency of the findings with the IDE study. The study limitations were that it was a single-arm study and that there were technical difficulties with the ultrasound scans.

PATIENT COUNSELING INFORMATION

The patient should be advised that Solesta treatment is not effective for all patients with FI and that repeat treatment might be required for treatment effect. It should also be made clear to the patient that the available clinical study data are not sufficient to predict in whom Solesta treatment will be effective. The patient should be informed about post-treatment care and potential adverse events. The patient should also be made aware that the implants might be detected during future anorectal and gynecological examinations and as well on radiographic imaging. Patients should be instructed to inform all future treating physicians about the presence of Solesta gel.

If there should be a need for future surgery (e.g., hemorrhoidectomy), the Solesta implant can be resected.

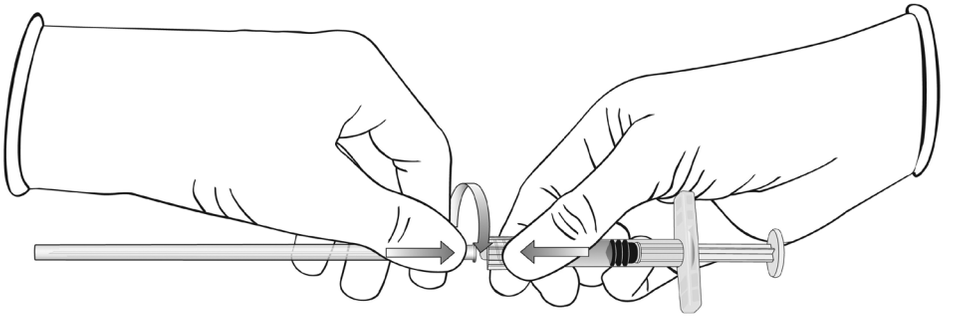
DIRECTIONS FOR USE

Solesta should be administered by qualified physicians with experience in the treatment of anorectal conditions and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure. Solesta should only be used after a thorough physical evaluation of the patient to exclude treatable underlying disorders.

For the safe use of Solesta, it is important that a new sterile needle is properly assembled and tightly fastened to each syringe.

Please note that the luer-lock adapter is snapped onto the syringe and held in place with friction only. It can rotate freely or be pulled off should enough force be applied. Because of this, it is recommended that the thumb and forefinger be held firmly around the luer-lock adapter on the glass syringe while attaching the needle to the syringe. DO NOT attach the needle by holding onto the glass barrel of the syringe. To facilitate proper threading/fastening of the needle hub and luer-lock adapter, please firmly **push and rotate** the needle hub into the luer-lock adapter as illustrated in Figure 5.

Figure 5: Proper Threading/Fastening of the Needle Hub and Luer-Lock Adapter

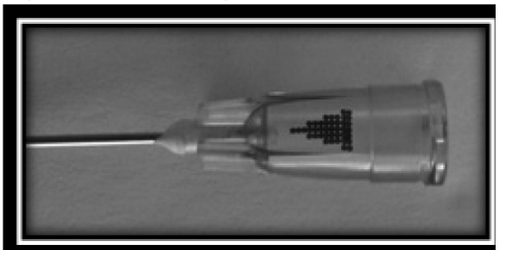


To avoid any interruption in patient treatment or the need to repeat a procedure because of leakage, or accidental contamination or damage of a syringe or needle, it is recommended that extra Solesta cartons be kept in inventory.

Method of Administration

1. The treatment is administered as an outpatient procedure without anesthesia.
2. Prior to treatment, the rectum should be evacuated with an enema. The enema should be given immediately prior to the procedure to ensure evacuation of the anorectum. Additional cleansing of the injection area with an antiseptic may be performed prior to injection.
3. Use of prophylactic antibiotics is recommended.
4. Four Solesta syringes should be made ready with mounted needles under aseptic conditions. Have small swabs and suction prepared and ready for use.
5. The patient is placed in the left lateral or prone position, and a lubricated anoscope is inserted. The obturator is removed and the anoscope withdrawn so that the dentate line is identified.
6. There is a triangular mark on the needle hub that provides the orientation of the needle bevel to ensure the bevel is facing the lumen when the needle is inserted (Figure 6).

Figure 6: Mark Indicating Needle Bevel Orientation



7. The four injections are to be given in the following order: posterior, left lateral, anterior, and right lateral.
8. The injections should be performed slowly to avoid stress on the luer-lock connection and allow the tissue to adapt to the injected gel.
9. Under direct vision, the mucosa is penetrated, approximately 5 mm proximal to the dentate line. The needle is advanced afurther 5 mm at approximately 30º to the axis of the rectum. If the patient indicates pain at the puncture, the injection site should be adjusted a few mm in the cephalic direction. If the puncture is painless, 1 mL of Solesta is injected in the deep submucosal layer. After injection, the needle should be kept in position for 15-30 seconds to minimize leakage of Solesta.
10. The injection is to be repeated at the remaining three injection sites. A new needle should be used for each syringe and injection site.
11. After completion of the four injections, the anoscope is extracted and the patient may rise. The patient should be instructed to rest at the clinic for approximately 60 minutes.

12. If no bleeding or other treatment related symptoms are observed during this time, the patient can be allowed to leave the clinic.
13. Confirming placement of Solesta gel by imaging may be of benefit.

Post-Treatment Care

1. The patient should be instructed to:
   - Contact the clinic or physician's office immediately if symptoms of rectal bleeding, bloody diarrhea, fever, tenesmus, or problems with urinating occur.
   - Avoid strenuous activity and taking hot baths during the first 24 hours post-treatment.
   - Avoid sexual intercourse and strenuous exercise for one week (e.g., horseback riding, bicycling, jogging, etc.).
   - Avoid anal manipulation for one month (e.g., insertion of suppositories or enemas and rectal temperature recording).
2. The patient should be informed of the risk of infections and bleeding.
3. Anti-diarrheal drugs should not be used for one week after treatment.
4. Stool softeners may be used until the first defecation occurs.
5. Analgesics other than non-steroidal anti-inflammatory drugs (NSAIDs) may be prescribed, if needed.

Re-Treatment Procedure

1. If the patient does not have an adequate response to Solesta after the first injection, a re-injection with a maximum of 4 mL Solesta can be performed, no sooner than four weeks after the first injection.
2. The re-treatment procedure and all pre-treatment preparations are performed the same way as the initial treatment procedure. All pre-treatment preparations and injection procedures should be performed as described in "Methods of Administration" above; however, the point of injection should be made in between the initial injections, shifted one-eighth of a turn (e.g., left posterolateral, left anterolateral, right anterolateral, and right posterolateral).

HOW SUPPLIED

Solesta is supplied in a glass syringe with a standard luer-lock fitting containing 1 mL gel. Each syringe is terminally moist-heat sterilized in a pouch. Four pouches, each containing one syringe, are packed in a carton together with four needles (21G x 4¾ inches, 0.80 mm x 120 mm) and patient record labels. The needles are sterilized by gamma irradiation.

STORAGE

Store at a temperature up to 25°C (77°F) and protect from sunlight and freezing.

Manufactured For:
Palette Life Sciences
Santa Barbara, CA 93101 USA

For product information, adverse event reports, and product complaint reports, please contact:
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